

found, for example, in original claim 5. Claims 21 and 23-37 are pending. The amendment does not introduce new matter.

Regarding rejection of the claims under 35 U.S.C. 112, first paragraph:

The claims were rejected under 35 U.S.C. 112, first paragraph, as being non-enabled by the specification, on the grounds that results of in vitro and animal studies do not correlate well with in vivo clinical results in patients. The office action stated that the successful operation of the claimed therapeutic method is unpredictable because:

- (1) the anti-B7.1 antibodies might be inactivated by proteolysis or immunological inactivation prior to having a therapeutic effect;
- (2) the anti-B7.1 antibodies might not be able to reach the targeted lymphoma cells; and
- (3) the anti-B7.1 antibodies might cause unexpected adverse side effects.

In support of the rejection, Dermer (1994) is cited as teaching that variation of human tumor cell lines contributes to chemotherapy's continued inefficacy against cancer; and Dillman (1994) is cited as teaching that no unconjugated monoclonal antibodies have proven therapeutic benefit in human hematologic malignancies or solid tumors.

The office action further states that it is unclear whether an antibody lacking a conjugated cytotoxic group can function as a "depleting antibody" as recited in claim 25, and calls for objective evidence that the claimed invention operates successfully, in view of the teaching by Falini et al. that an anti-CD30 antibody that binds lymphoma cells has no anti-tumor effect.

The office action further states that the specification does not disclose conjugated B7-specific antibodies.

The Applicants respectfully traverse the rejection of the claims under 35 U.S.C. 112, first paragraph, as being non-enabled by the specification.

Support for the therapeutic efficacy of the anti-B7.1 antibodies of the present invention is provided by clinical studies in which anti-B7.1 antibodies such as those of the claimed invention are administered to human patients to treat psoriasis. For example, Gottlieb et al. (J. Am. Acad. Dermatol., 2002, 47(5):693-700; also, J. Invest. Dermatol., 2000, 114(4):840, abstract # 546, copies attached) reports that anti-B7.1 antibodies administered to

human patients suffering from psoriasis are relatively stable in vivo, with serum half-life of approximately 13 days (p. 696), and that patients receiving single intravenous infusions of from 0.05 to 15 mg per kg experienced only mild or moderate side effects(pp. 696-698). The references also report that there is preliminary evidence that the anti-B7.1 antibodies have therapeutic clinical activity in the higher dosage groups. The target cells of the anti-B7.1 antibodies for treatment of psoriasis are antigen-presenting cells (APCs), whereas the target cells of the claimed invention are B lymphoma cells. The Applicants respectfully submit that persons skilled in the art would reasonably regard the demonstration in Gottlieb et al. that anti-B7.1 antibodies have stability in vivo and clinical activity in a method targeting APCs as evidence that the anti-B7.1 antibodies are also likely to show similar stability and ability to bind to target cells in the claimed method.

The stability and ability of anti-B7.1 antibodies to bind to interact effectively with target B lymphoma cells is demonstrated by the attached in-house manuscript by Drs. Kandasamy Hariharan and Nabil Hanna. This manuscript describes results that show that unconjugated anti-B7.1 antibodies operate successfully in vitro and in vivo to inhibit the growth of and/or kill B cell lymphoma cells. IDEC-114 is a primatized anti-B7.1 antibody that has the light and heavy chain variable regions of 16C10. Figures 2(a) and 2(b) show that IDEC-114 induces antibody-dependent cellular cytotoxicity (ADCC) of SB and SKW lymphoma cells in vitro with concentration-dependent activity that is comparable to the activity of rituximab (p. 10); and Figure 3 shows that combinations of IDEC-114 antibody and rituximab act cooperatively to induce significantly greater levels ADCC of SKW lymphoma cells than equivalent amounts of either antibody alone (p. 11). Figure 5 shows that administration of the IDEC-114 antibody to SCID mice inoculated with SKW lymphoma cells increases the survival time of the treated mice with activity comparable to the activity of rituximab (p. 15); and Figure 6 shows that combinations of IDEC-114 antibody and rituximab act cooperatively to induce significantly increased survival of SCID mice inoculated with SKW lymphoma cells relative to the survival of mice treated with equivalent amounts of either antibody alone (p. 16). Rituximab is a chimeric antibody that has human constant regions and the variable regions of a murine anti-CD20 antibody. Rituximab operates effectively in vivo as a B cell depleting agent with therapeutic, anti-lymphoma activity (see,

for example, U.S. Patent No. 5,776,456); and is approved by the Food and Drug Administration for administration to human patients suffering from a B cell lymphoma.

The office action asserted that the activity of the anti-B7.1 antibodies of the present invention is unpredictable because they might be proteolyzed or otherwise inactivated prior to having a therapeutic effect, and because they might be unable to reach the targeted lymphoma cells. The Applicants respectfully submit that in view of the similarity in structure and activity in vivo and in vitro of anti-B7.1 antibodies and rituximab, persons skilled in the art would reasonably expect that the anti-B7.1 antibodies of the present invention would have stability in vivo that is on the order of that of rituximab, and ability to reach the targeted lymphoma cells that is also comparable to that of rituximab. The anti-B7.1 antibodies of the present invention target B cells bearing B7.1 antigen on their surface; whereas rituximab targets B cells bearing CD20 antigen. Given the similarity of the targeted cells, persons skilled in the art would also reasonably expect that side effects of administering the anti-B7.1 antibodies of the present invention would be similar to those of rituximab. Accordingly, persons skilled in the art would reasonably expect the anti-B7.1 antibodies of the present invention to have stability, ability to reach target lymphoma cells, and side effects, that are comparable to those of rituximab, which has proven therapeutic efficacy against B cell lymphoma.

It is well established that when a claimed pharmacological agent is similar in structure to a compound that has therapeutic activity in human patients, and the claimed agent also operates in vitro and/or in vivo with activities that are similar to those of the proven therapeutic agent, it is reasonable for one skilled in the art to expect that the claimed pharmacological agent will also be therapeutically active in human patients. See for example, *In Re Brana* (34 USPQ2d 1436, Fed. Cir., 1995), in which a compound with antitumor activity in vitro was found to be patentable, in view of the similarity of its chemical structure and activities to those of compounds known to be active as antitumor drugs. In its decision, the Federal Circuit pointed out that although the claims had been rejected under 35 U.S.C. § 101, the rejection was essentially based on 35 U.S.C. § 112, 1st paragraph, and they addressed the question of patentability as if the claims had been rejected for non-enablement under 35 U.S.C. § 112, 1st paragraph.

The office action also asserted that the anti-B7.1 antibodies of the present invention The error of this assertion is shown by the experimental results disclosed in the attached manuscript of Drs. Hariharan and Hanna, which describes the induction of cytotoxicity of B cell lymphoma cells by anti-B7.1 antibodies in vitro, and the prolongation of survival of SCID mice inoculated with lymphoma cells by anti-B7.1 antibodies in vivo, with activities comparable to those of rituximab. Rituximab is an unconjugated, chimeric monoclonal antibody that binds specifically to a B cell epitope and has therapeutic activity against B cell lymphoma. The assertion that persons skilled in the art would consider it necessary for conjugated anti-B7.1 antibodies to be conjugated to a cytotoxic agent in order to have therapeutic activity against B cell lymphoma is not correct. While not committing to any particular mechanism of activity, a molecular physiological basis for the therapeutic activity of the unconjugated anti-B7.1 antibodies against lymphoma cells in vivo is indicated by a recently published article by Suvas et al., which shows that anti-B7.1 antibodies retard the growth of lymphoma cells in vitro, and up-regulate the pro-apoptotic molecules caspase-3, caspase-8, Fas, FasL, Bak, and Bax, while down-regulating the anti-apoptotic molecule Bcl-x(L) (J. Biological Chemistry, 2002, 277(10):7766-7775, copy attached).

In accord with the foregoing, one skilled in the art would reasonably expect to be able to follow the teachings of the specification and successfully use the claimed method for treating a B cell lymphoma without having to perform undue experimentation. The Applicants therefore respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for non-enablement be withdrawn.

Regarding rejection of claim 24 under 35 U.S.C. 112, second paragraph:

Claim 24 was rejected as being indefinite because the characteristics of the recited antibodies are not known. The Applicants strongly traverse the grounds for the rejection. The specification clearly identifies detailed characteristics of each of the recited antibodies, including their amino acid sequences. However, in order to expedite prosecution, claim 24 is amended to recite a method wherein the anti-B7.1 antibody binds the same epitope as anti-B7.1 antibody 16C10, which has the variable sequences shown in Figures 10a and 10b (amino acid sequences of SEQ ID NOs. 9-10 and 11-12 respectively). Claim 23 is similarly amended to recite amino acid and nucleotide sequences of the recited antibodies. Withdrawal

of the rejection for indefiniteness under 35 U.S.C. 112, second paragraph, is respectfully requested.

Regarding rejection of the claims under 35 U.S.C. 103(a):

The claims were rejected under 35 U.S.C. 103(a), as being obvious in view of U.S. Patent No. 5,304,635 (Imam et al.), in view of Delabie et al. (1993), and/or Munro et al. (1994), and Falini et al. (1994). The Applicants respectfully traverse the rejection. None of the cited references describes or suggests using anti-B7.1 antibodies to treat B cell lymphoma.

The Imam et al. patent describes antibodies against BLA-36, but does not disclose or suggest making or using anti-B7.1 antibodies or suggest that unconjugated antibodies could be used for therapy.

Falini et al. discloses antibodies against CD30, but also does not suggest making anti-B7.1 antibodies or administering them to kill or inhibit the growth of lymphoma cells in a patient with lymphoma.

Likewise, neither Delabie et al. nor Munro et al.. discloses or suggests that anti-B7.1 antibodies could be used to kill or inhibit the growth of lymphoma cells in a patient with lymphoma.

The combination of prior art references could only have provided one skilled in the art with a suggestion to try the claimed method; however, it could not have provided one skilled in the art with any reasonable expectation of success. "Obvious to try" is not the standard for supporting an obviousness rejection under 35 USC 103. See In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). More than this is required to establish *prima facie* obviousness. Under U.S. patent law, a suggestion or motivation to combine various teachings of prior art references to obtain the claimed invention, and a reasonable expectation that the combination will operate successfully, must be found in the prior art, not in applicant's disclosure. See M.P.E.P. § 2143, Basic Requirement of a Prima Facie Case of Obviousness, citing In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The inventors of the present application are the first to disclose that the claimed method can be used successfully to treat B cell lymphoma. Given that the claimed invention is neither described nor suggested by the prior art, and that those skilled in the art in view could not have predicted that the claimed invention would operate

successfully, the Applicants respectfully request that the rejection of the claims under 35 U.S.C. 103(a) be withdrawn.

It is believed that the foregoing amendment has fully addressed the points raised in the official action, and that the application is now in condition for allowance. Early notice to this effect is respectfully requested.

Respectfully submitted,
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APPENDIX

Claims 21, 23, 24, 32, and 33 are amended as shown below:

21. (Amended) A method of treating B cell lymphoma comprising administering a therapeutically effective amount of an [anti-B7] anti-B7.1 antibody.
23. (Amended) The method of claim 21 wherein said [B7 is B7.1] antibody binds the same epitope as an anti-B7.1 antibody selected from the group consisting of 7C10, which has the variable sequences shown in Figures 8a and 8b (amino acid sequences of SEQ ID NOs. 1-2 and 3-4 respectively); 7B6, which has the variable sequences shown in Figures 9a and 9b (amino acid sequences of SEQ ID NOs. 5-6 and 7-8 respectively); and 16C10, which has the variable sequences shown in Figures 10a and 10b (amino acid sequences of SEQ ID NOs. 9-10 and 11-12 respectively).
24. (Amended) The method of claim [21] 23 wherein [said anti-B7] the anti-B7.1 antibody binds the same epitope as [an anti-B7.1] antibody [selected from the group consisting of] 16C10, [7C10, 20C9 and 7B6] which has the variable sequences shown in Figures 10a and 10b (amino acid sequences of SEQ ID NOs. 9-10 and 11-12 respectively).
32. (Twice Amended) The method of claim 21 wherein the antibody is a primatized antibody having the variable sequences [regions of the 16C10 antibody wherein said antibody] of an anti-B7.1 antibody selected from the group consisting of 7C10, which has the variable sequences [contained] shown in Figures 8a [-] and 8b ([the] amino acid sequences [by] of SEQ ID NOs. [1 and 2 and 3 and 4] 1-2 and 3-4, respectively)[,]; 7B6, which has the variable sequences shown in Figures 9a [-] and 9b [8b] ([the] amino acid sequences [by] of SEQ ID NOs. [5 and 6 and 7 and 8] 5-6 and 7-8, respectively); and 16C10, which has the variable sequences shown in Figures 10a [-] and 10b [8b] ([the] amino acid sequences [by] of SEQ ID NOs. [9 and 10 and 11 and 12] 9-10 and 11-12, respectively).

33. (Amended) The method of claim 21 wherein the [anti-B7] anti-B7.1 antibody is a monoclonal antibody [that specifically binds human B7.1,] having a human gamma 4 constant domain.